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TOLERANCE TO EFFECTS OF COCAINE ON BEHAVIOR UNDER A RESPONSE-INITIATED FIXED-INTERVAL SCHEDULE

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Tolerance to effects of cocaine can be modulated by schedules of reinforcement. With multiple ratio schedules, research has shown an inverse relationship between ratio requirement and amount of tolerance that resulted from daily administration of the drug. In contrast, tolerance to the effects of cocaine on behavior under multiple interval schedules generally has developed regardless of interval value. Under interval schedules reinforcement depends on the animal making one response following a time interval. Thus, as time to respond increases, the time to reinforcement decreases. On the other hand, fixed ratio schedules require a specified number of responses to be made prior to reinforcement. Therefore, delaying the initiation of responding does not coincide with a significant decrease in the time to reinforcement. In the current experiment, 6 pigeons were trained to respond under a three-component multiple schedule, with a different tandem fixed-ratio 1 fixed-interval schedule in each component. The multiple schedule required one response, which was followed by one of three fixed-interval values (5, 15, or 60 s). Thus, the multiple schedule was interval-like because after the fixed-ratio 1, only one more response was required for reinforcement, but it was also ratio-like because the length of the pause at the beginning of each interreinforcer interval affected the time until the next reinforcer. Acute administration of cocaine generally resulted in dose-dependent decreases in responding. Chronic (i.e., daily) administration of a rate-decreasing dose resulted in tolerance patterns similar to those usually obtained with multiple ratio schedules. That is, the magnitude of tolerance was related inversely to schedule size. These results suggest that delay to reinforcement from the initial response may play a role in the development of schedule-parameter-related tolerance.

Key words: cocaine, tolerance, fixed-interval schedules, fixed-ratio schedules, tandem schedules, key peck, pigeons

Drug tolerance is characterized by three features: (1) it often occurs after repeated or prolonged exposure, (2) it is revealed as a loss of effect relative to the drug's initial impact, and (3) in most cases, more of the substance is required to attain the initial effect (Carlton, 1983; Rang, Dale, Ritter, & Moore, 2003). Tolerance can be illustrated as a shift to the right of the dose–response function, and has been implicated as a contributing factor to drug abuse and is also of concern for clinical therapeutics (O'Brien, 2001).

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Previous research has illustrated that environmental circumstances may play a significant role in the development of tolerance (for reviews see Branch, 1991; Carlton, 1983; Stewart & Badiani, 1993; Wolgin, 1989). For example, contingencies of reinforcement can influence drug tolerance (e.g., Branch, 1990; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991; Hughes, Sigmon, Pitts, & Dykstra, 2005; Nickel, Alling, Kleiner, & Poling 1993; Pinkston & Branch, 2004; van Haaren & Anderson, 1994; Yoon & Branch, 2004). As an illustration, Hoffman et al. (1987) studied the development of tolerance to effects of cocaine on behavior under a multiple fixed-ratio (FR) schedule with FR values of 5, 25, and 125 (FR 50 for one subject). Initially, injections of cocaine prior to experimental sessions resulted in dose-dependent decreases in keypecking. With daily presession administration of a dose of cocaine that decreased response rates, tolerance to these behavioral effects developed under the FR 5 schedule, but did so less or not at all under the larger value FR schedules. This finding may be referred to as schedule-parameter-related tolerance, and has been

obtained in a variety of species (Hughes & Branch, 1991; van Haaren & Anderson, 1994), with different drug types (Hughes et al., 2005; Nickel & Poling, 1990), and with different types and values of ratio schedules (Branch, 1990; Nickel et al., 1993; Yoon & Branch, 2004). These findings have led to subsequent studies attempting to clarify behavioral mechanism(s) involved in producing schedule-parameter-related tolerance.

In most cases, the rate of reinforcement is greater with short FR schedules than long, so reinforcement rate may be a key variable in producing the phenomenon. Schama and Branch (1989) directly examined the role of reinforcement rate by exposing pigeons to a three-component multiple fixed-interval (FI) schedule, in which the FI values (FI 5, 20, and 120 s) approximated baseline rates of reinforcement obtained in the Hoffman et al. (1987) study. In contrast to the previous study with FR schedules, roughly equivalent amounts of tolerance developed for all three FI schedule parameters. These findings suggested that schedule-parameter-related tolerance was not a result of differences in baseline rates of reinforcement.

One major difference between FI and FR schedules is the response requirement. Namely, the number of responses required by an FR schedule is the FR value. In contrast, an increase in FI schedule parameter increases the minimum time between reinforcements without a change in the single response requirement at the end of the FI, although the number of responses per reinforcement generally increases as FI duration increases (Ferster & Skinner, 1957). Another result of increased FR values is that, if response rate does not change, the time from the first response to delivery of the reinforcer also increases. In contrast, the time delay from response initiation until reinforcer delivery does not necessarily increase with FI parameter, although it usually does.

A second difference between FI and FR schedules, one that was a focus of the research described here, is the manner in which a postreinforcement pause (PRP) termination is related to the delay to the ensuing reinforcer. The PRP is defined as the latency to begin responding once the discriminative stimulus has been presented. In the case of FI schedules, the relationship between PRP and reinforcement creates a contingency wherein a long PRP is associated with a shorter delay from the first response to the next reinforcer. In addition, the length of the PRP generally does not influence overall rate of reinforcement (except in the infrequent instance when the PRP exceeds the interval value). These relationships do not hold for FR schedules. As long as rate of responding remains unchanged, a long PRP under an FR schedule does not affect the time from the first response until the next reinforcer. A further distinction from interval schedules is that an increased PRP decreases rate of reinforcement.

The above differences in contingencies between pause termination and reinforcement on FR and FI schedules were examined indirectly by Capehart, Eckerman, Guilkey, and Shull (1980), who reported that the probability of pause termination increased with time after reinforcement under FI schedules but not under FR schedules. That difference suggests that the contingency between PRP duration and delay to reinforcement, that is present in FI schedules, influences the latency to PRP termination in such schedules. Conversely, no such relation between length of a PRP and the probability of its termination exists for FR schedules.

The current study was based on the possibility that schedule-parameter-related tolerance depends on the independence of PRP duration and delay to reinforcement on FR schedules. Our approach involved an FI schedule designed to make the relation between delay to reinforcement and PRP termination FR-like, while retaining an FI-like response requirement. This was achieved by making the start of the FI contingent on a response. This schedule arrangement is technically a tandem FR 1 FI, but is often referred to as a response-initiated fixed-interval (RIFI) schedule (Mechner, Guevrekian, & Mechner, 1963; Shull, 1970). Under such a procedure, the response that ends the PRP begins the FI. The only other required response is the one that results in reinforcement.

The present study employed three parameters of RIFI schedules in the context of a multiple schedule in which a distinct visual stimulus was associated with each schedule component. In addition, the schedule was arranged to have equal numbers of reinforcers delivered in each component. Such an

arrangement allowed us to determine if a schedule that has interval-like contingencies at the moment of reinforcement, but which also mimics the relation between PRP termination and subsequent delay to reinforcement under FR schedules, would result in schedule-parameter-related tolerance to effects of cocaine.

METHOD

Subjects

The study included 6 experimentally naive adult White Carneau pigeons (*Columba livia*); 3 females (44, 4455, 642) and 3 presumed males (i.e., none produced eggs during or after the completion of the current study; 680, 657, 611). All subjects were maintained at 80% of their ad libitum weights. Animals were individually housed in a colony room, with free access to water and grit. The colony room was kept at constant temperature and humidity, with a light/dark cycle of 16:8 hours, with lights on at 7:00 am and lights off at 11:00 pm.

Apparatus

Experimental sessions were conducted in a BRS/LVE (Model 9381-D) chamber. Inside dimensions of the chamber were 35 × 31 × 35 cm. One wall contained three horizontally aligned translucent plastic response keys. The keys were 8 cm from the ceiling and had a diameter of 2.5 cm. Illumination for keys was provided by IEE One-Plane Readouts (Model Number 00010-01-0K21-1820) with 1.1-W lamps. Only the center key was used during this experiment. Pecks of at least 0.25 N were required for a response to be recorded. Each response produced one 30-ms, 2900-Hz tone from a Mallory® Sonalert. A 6 × 5-cm opening was positioned 9 cm below the center key. Mixed grain could be made available to the pigeon through this hole by the operation of a solenoid-operated feeder, which could be illuminated by a 1.1-W lamp. Another 1.1-W lamp, the house light, was positioned centrally, 2 cm from the top of the wall. Extraneous sounds were masked by 95-dB white noise in the room where the chamber was located. Programming and recording of experimental events was performed by a custom-built computer (Palya & Walter, 1993).

Behavioral Procedure

All animals were trained to eat from the feeder, and key pecking was shaped by reinforcing successive approximations of the terminal response. Key pecking was established in the presence of a white key light. Reinforcement consisted of 3-s access to the food. When food was available, the aperture was illuminated, and all other lights in the chamber were extinguished. After key pecking was established under an FR 1 schedule with a white key light, two more stimulus colors were included. Reliable responding on the FR 1 schedule took one to two sessions, which consisted of 45 key-light stimulus presentations per session. Initially, the training-session design was a three-component multiple FR 1 schedule with the white key light stimulus for 20 food presentations, followed by 15 presentations associated with a blue key light, and 15 in the presence of the red key light. The color training process lasted for two sessions for Subject 44, but only one session for the rest of the subjects. Once responding in the presence of all stimulus lights was established, the order of the three different stimulus lights was changed to randomly present each color 15 times (45 total) per session. Once key pecking was reliably established, the subjects began an FI training regimen. This regimen included a gradual increase of FI values in the context of the correlated stimulus lights. Initially, the pigeons were exposed to a multiple FI 5-s, FI 5-s, FI 5-s schedule. Sessions consisted of presenting the colors in randomized blocks of three until 45 food presentations had occurred or one hour had elapsed. The schedule was subsequently increased to FI 15-s, and then increased in 15-s increments until responding reliably occurred in the context of an FI 60-s schedule for each color. Increases in FI value occurred when visual inspection of responding showed stability. The training regimen to this point lasted between 12 and 22 sessions with a median of 17 sessions.

The final schedule was a three-component multiple RIFI schedule, with parameter values in the different components of 5, 15, and 60 s. The values were chosen because they are roughly 50% of the FI values employed by Schama and Branch (1989). Prior research suggests that the average PRP for fixed-interval schedules is roughly 50% of the interreinforcement interval (Powell, 1968; Schneider,

1969; Shull, 1971; Zeiler & Powell, 1994). The RIFI 5-s component was correlated with a white key light, the RIFI 15-s component with blue, and the RIFI 60-s component with red.

Experimental sessions occurred once daily, at roughly the same time, 7 days a week. Sessions were divided into three blocks of three components each, with each component lasting for four presentations of one RIFI schedule value, or until a time limit expired (see below). Each component occurred once per block, with the order of presentation of the three schedule values determined randomly in each block. Components were separated by 30-s blackouts, during which all programmed stimuli were extinguished, and responses were not recorded. Sessions began with a 5-min blackout period, followed by the illumination of the center key with one of the three stimulus lights.

Time limits were in place for each component. The limits were 60, 180, and 720 s, for the RIFI 5-s, RIFI 15-s, and RIFI 60-s components, respectively. The time limits were all 12 times the FI component value and were intended to give the animal ample time complete four cycles of the RIFI schedule. If a time limit was reached the current component was terminated, a 30-s blackout period occurred, and the next component was presented. The time limits ensured that the subject would be exposed to all schedule components in each session, regardless of response rates. The time limits set the maximum session length to 57.5 min including blackout periods (9.5 min), though a typical session lasted roughly 30 min.

Initial baseline conditions continued until stable key pecking was established. Behavior was deemed stable if there were no apparent trends revealed by visual inspection of daily session average response rates for the final 10 days of the phase. After a consistent baseline was established, pharmacological procedures began (described below). It took between 69 and 106 days to establish a consistent baseline of responding.

Pharmacological Procedures

Cocaine hydrochloride (obtained from the National Institute on Drug Abuse) was dissolved in 0.9% saline solution and delivered by intramuscular injection into the breast. The cocaine injection volume was held constant at 1.0 ml/kg of the subject's experimental weight. Injections were administered immediately prior to experimental sessions. When injections occurred before successive sessions, the site of injection was alternated daily between the left and right breasts. Doses ranged from 1.0 to 23.0 mg/kg. It should be noted that changes in University of Florida's Institutional Animal Care and Use Committee's (IACUC) approved dosing limits were made after the majority of subjects had completed the experiment. This policy change precluded the inclusion of doses greater than 10.0 mg/kg for the dose–response function of Subject 4455.

Prechronic (acute) dose determinations. Daily sessions continued and pigeons were injected with a dose of cocaine immediately before each seventh session. Doses of 10.0, 5.6, 3.0, and 1.0 mg/kg of cocaine, as well as the saline vehicle, were injected in that order twice so that systematic changes across repeated administrations would be easier to discern (cf. Sidman, 1960). No such changes were observed. When successive administrations of a given dose produced inconsistent effects, the dose was administered until the mean effect was representative. Doses of cocaine up to 23.0 mg/kg were administered to determine the effects of cocaine on responding; doses outside of the range mentioned above were administered as needed. The length of the initial acute drug-assessment phase varied widely across subjects and lasted 97, 99, 121, 132, 169, and 294 sessions for Subjects 680, 642, 611, 657, 44, and 4455, respectively.

Chronic dose administration. For each pigeon, a dose of cocaine that decreased, but did not completely suppress behavior was chosen for chronic administration. This dose varied across subjects in an attempt to use a functionally similar (rather than numerically identical) dose for repeated administration. During chronic administrations, injections occurred on a daily basis, immediately prior to the beginning of the session. For all subjects chronic-dose administration occurred initially for a minimum of 50 daily sessions and until effects appeared stable from day to day. Stability was defined as the absence of any increasing or decreasing trends in daily response-rate data for 10 days. Subjects 680, 642, and 4455 received 5.6 mg/kg for 54, 50, and 50 sessions respectively. Subject 44 received

4.2 mg/kg for 87 sessions, and Subject 611 received 10.0 mg/kg for 50 sessions. Subject 657 initially received 7.4 mg/kg for 34 sessions. This dose completely suppressed key pecking; therefore, the daily dose was reduced to 5.6 mg/kg, and 50 additional sessions were completed before additional testing began.

Dose–response determinations during chronic administration. Once 50 sessions had been conducted and stability in response rates was maintained, the effects of cocaine on responding were again assessed in the context of continued daily administration of the chronic dose. This assessment was accomplished by administering probe doses, once every seventh day, that were the same as, or in some instances greater than those administered during the acute-dose determination phase. The larger doses allowed for a more complete characterization of the chronic dose–response function. Procedurally, this phase resembled the acute phase in every manner, except that the chronic dose continued to be injected prior to each of the 6 sessions between probe doses. The dose–response assessments during chronic administration lasted from 66 to 160 sessions across subjects with a median of 111 sessions.

Data Analysis

The main dependent measure was response rate, expressed as a percentage of rates observed when the saline vehicle was administered. Responding following saline administration was consistent within, but different between phases, and the differences were unsystematic across pigeons and multiple-schedule components (See Appendix.). Therefore, the response-rate data were normalized to illustrate more clearly the effect that drug doses had when compared to the saline control data. Normalized response rate was plotted over dose, yielding dose–response functions. Such functions were independently constructed for each component of the multiple schedule, and separately for each pigeon.

For some analyses, estimates of the dose that effectively decreased response rates by 50%, (ED_{50}), were calculated by fitting a negative sigmoid logistic to the collected data (SigmaPlot 9.0®). In cases where there were no points below 50% of the saline baseline a response rate was set to zero at a dose that was 1/8 log unit greater than the largest dose actually administered. This estimation of the zero-response dose was chosen because it provided a conservative estimate of the magnitude of tolerance in components that were associated with the most tolerance. Thus, if differential tolerance was observed as predicted, the differences would be underestimated. The use of a hypothetical dose was designed to avoid possible harm (via overdose) to the animal subjects and provide a means to calculate the ED_{50} value for the chronic dose–response functions.

The analysis and discussion of drug/parameter effects were directed primarily by visual analysis of graphically arranged individual-subject data. For some measures supplementary inferential statistical analyses were performed on the group-aggregate data. Inferential statistical analysis included repeated measures analysis of variance (ANOVA) tests for the effects of cocaine on normalized response rates as well as on the ED_{50} calculations.

RESULTS

Because analyses of within-session changes in behavior revealed that drug effects were consistent within sessions, session totals were used for the following analyses. Effects of the RIFI schedules on performance, prior to the administration of drugs, are summarized in Table 1, which presents data collected from the final five sessions of baseline conditions for each subject. Generally, as the duration of the RIFI schedule increased, interreinforcement interval (IRI), PRP, and total responding also increased, while response rate and running rate (response rate exclusive of PRP time) decreased. The proportion of IRI spent PRP was shortest in the middle-valued component (RIFI 15 s) for most subjects. Some subjects exhibited the highest response-rate and running-rate data in this component. Specifically, response rates were greatest in the RIFI 15-s component for 3 subjects (4455, 657, 680), and the RIFI 15-s component also yielded the highest run rates for the 3 subjects.

Prechronic Effects of Cocaine on Response Rates

The prechronic (i.e., acute) effects of cocaine administration on responding are illustrated by filled circles in Figure 1, which shows normalized response rates as a function of dose. Dose–response functions generally

Table 1

Means from the last 5 days of baseline.

	RIFI 5 s	RIFI 15 s	RIFI 60 s	RIFI 5 s	RIFI 15 s	RIFI 60 s
Subject	Interreinforcement Interval (s)			Postreinforcement Pause (s)		
680	6.78	17.76	86.14	1.15	2.11	25.02
642	7.14	18.12	81.72	2.05	2.87	19.83
611	6.64	17.42	87.62	1.41	2.02	28.28
657	7.20	17.64	81.44	1.71	2.33	19.17
44	7.20	19.52	92.38	1.49	4.00	31.81
4455	6.90	17.60	85.45	1.26	2.37	21.32
	Total Pecks			**PRP/IRI**		
680	8.42	27.44	88.50	0.17	0.12	0.29
642	21.82	41.20	74.06	0.29	0.16	0.24
611	16.04	42.86	70.38	0.21	0.12	0.32
657	9.86	34.38	106.66	0.24	0.13	0.24
44	10.22	21.96	43.60	0.21	0.20	0.34
4455	7.48	22.12	33.46	0.18	0.13	0.25
	Response Rate (r/s)			**Running Rate ((r−prp)/s)**		
680	1.24	1.55	1.03	1.50	1.75	1.45
642	3.06	2.27	0.91	4.29	2.70	1.20
611	2.42	2.46	0.80	3.07	2.78	1.19
657	1.37	1.95	1.31	1.79	2.25	1.71
44	1.42	1.13	0.47	1.79	1.41	0.72
4455	1.08	1.26	0.39	1.33	1.45	0.52

exhibited a dose-dependent decrease in response rates, although in a few cases smaller doses consistently resulted in increased responding above the range of vehicle effects (most commonly in the RIFI 60-s component). Responding was completely suppressed or at near zero levels (i.e., less then 5% of saline responding) for all subjects when a 10.0 mg/kg dose was administered, with the exception of Pigeon 611. Responding for Pigeon 611 was never completely suppressed by any of the test doses, including 13.0 and 17.0 mg/kg; the form of the dose–response function for this subject, however, was a dose-related decrease in response rates during the two shorter-interval components, and an increase followed by a decrease in the long-interval component. There was intersubject variation in sensitivity to rate-decreasing effects, with Pigeon 44 being the most sensitive and Pigeon 611 the least. Overall, however, the forms of the dose–response functions, especially the decreasing portions, were similar across components of the multiple schedule.

Chronic Effects of Cocaine on Response Rates

The open symbols of Figure 1 show that response rates generally decreased dose-dependently during chronic administration of a rate-decreasing dose of cocaine. Chronic drug exposure tended to decrease the slopes of the dose-effect curves compared to those obtained during acute exposure. Moreover, in contrast to acute effects, there was a more pronounced effect of schedule component (especially apparent for Subjects 657, 44, and 4455), exhibited by a tendency for greater decreases in response rates in the RIFI 60-s component at the larger doses than in the RIFI 5-s component. During chronic drug administration all subjects responded at the 10.0 mg/kg dose in all three schedule components, so larger doses were tested.

Another change in the dose–response functions following repeated administration was that very few doses of cocaine generated mean rates of responding that exceeded saline baseline levels. Interestingly, no consistent increases were seen in the RIFI 60-s component, the component where increases had been most common following prechronic administrations (Subjects 657, 44, 642, & 611).

Figure 1 includes both prechronic and chronic assessment data expressed as percent of vehicle responding, and therefore, allows for a direct comparison of schedule component dose–response functions before and after repeated administration. This comparison reveals shifts to the right in the chronic

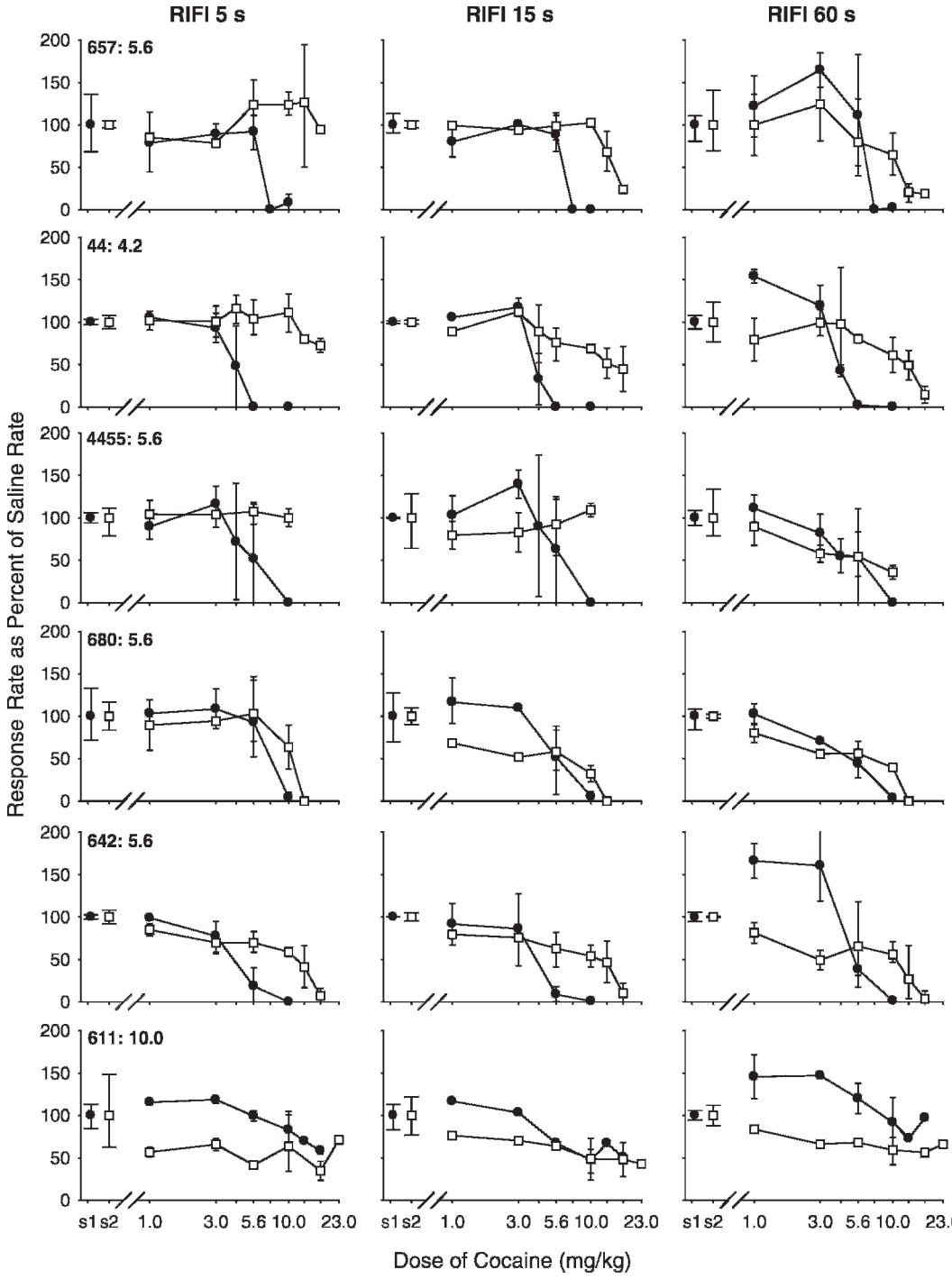

Fig. 1. Response rate averaged over the entire session, as a percentage of saline control, as a function of dose of cocaine. Each row shows the data of one subject. Each column shows data from one of the three schedule durations. Filled circles depict average response rates with acute dosing and open squares depict average response rates during chronic dosing. Vertical bars show ranges. Saline vehicle responding for the acute and chronic phases are represented above s1 and s2 respectively. Unlabeled tick marks correspond to 4.2, 7.4, 13.0, and 17.0 mg/kg, respectively, as they appear from left to right on the X-axis. Doses of cocaine are scaled logarithmically on the X-axis.

functions for 5 of 6 subjects. The chronic dose–response functions for Pigeon 611 shifted to below the prechronic function, with many doses that were previously inactive decreasing response rate during chronic administration. The visual impression of the data for the remaining subjects (i.e., 657, 44, 4455, 642, 680) shows that shifts were larger for the smaller RIFI components, thus tolerance was more pronounced for them.

A three-way repeated-measures ANOVA comparing dose, regimen (acute vs. chronic), and schedule duration (RIFI 5 s, 15 s, or 60 s) was performed for the 5 subjects that exhibited tolerance to the decreases in response rates. The ANOVA was limited to effects of doses that were administered to all subjects (1.0, 3.0, 5.6, 10.0 mg/kg), and was performed using the mean effect for each pigeon at each dose. The ANOVA yielded statistically significant differences for dose, $F(3, 15) = 30.334$, $p < 0.01$, which reflects the dose-dependent decreases seen in Figure 1. A significant interaction of dose and regimen, $F(3, 15) = 19.642$, $p < 0.01$, was also obtained, which is consistent with an effect of chronic administration. That is, the dose-by-regimen interaction statistically supports a difference in dose-effect curves, consistent with tolerance. A significant interaction between schedule duration and regimen, $F(2, 10) = 6.501$, $p < .05$, was also obtained, and supports the view that the schedule duration modulated the magnitude of tolerance. Overall, the results of the ANOVA are consistent, on a group-aggregate level, with the individual subject data that are displayed in Figure 1.

Figure 2 presents ED_{50} values for both acute and chronic dose-effect assessments. Two features should be noted; first, inspection of the black bars within each frame show that ED_{50} values were similar across the three components, indicating that schedule duration had little influence on the effects of cocaine on response rates, prior to the chronic administration. Second, comparison of gray and black bars within subject and across schedule durations reveals that chronic administration led to a greater increase in ED_{50} value with RIFI 5 s as compared to the RIFI 60 s for all 5 pigeons that showed tolerance. A two-way repeated measures ANOVA examining regimen and schedule duration was performed using data from the 5 pigeons that showed tolerance. There were statistically significant effects of regimen, $F(1, 4) = 8.079$, $p < .05$, schedule duration, $F(2, 8) = 8.441$, $p < .05$, and the interaction between regimen and schedule duration, $F(2, 8) = 11.143$, $p < .05$. The statistical tests support the assertion that at the group-average level there was a difference in the ED_{50} values in the prechronic and postchronic assessments. They also support the view that the drug effects were influenced by schedule duration and, most importantly, that tolerance was related to schedule duration.

DISCUSSION

Examination of dose-response functions and ED_{50} values revealed tolerance to the rate-decreasing effects of cocaine for 5 of 6 subjects. Furthermore, tolerance to the rate-decreasing effects was related to schedule duration. Specifically, tolerance reliably developed in the RIFI 5-s component, whereas less developed in the RIFI 60-s component. Tolerance in the RIFI 15-s component developed to varying degrees across subjects, but most often resembled that in the RIFI 5-s component. That is, tolerance was related to schedule size. Therefore, this study extends findings typically associated with ratio schedules of reinforcement (Hughes & Branch, 1991; Hughes, et al., 2005; Nickel & Poling, 1990; Nickel, et al., 1993; van Haaren & Anderson, 1994) to RIFI schedules of reinforcement.

Like the study by Hoffman et al. (1987), in which a multiple fixed-ratio schedule was used, the PRP under the current RIFI schedules was (1) directly related to the time to the next reinforcement, and (2) inversely related to the overall rate of reinforcement. These are necessary features of all ratio schedules, and are common to arrangements that have consistently yielded parameter-related tolerance (e.g., Hughes & Branch, 1991; Hughes, et al., 2005; Nickel, et al., 1993; Nickel & Polling, 1990; van Haaren & Anderson, 1994). Further, neither of these relationships is present in FI or variable-interval (VI) schedules (except in the relatively rare cases where the pause exceeds the interval value), schedules under which parameter-related tolerance is typically not obtained. The relationship between pause termination and delay to reinforcement therefore appears to be a key

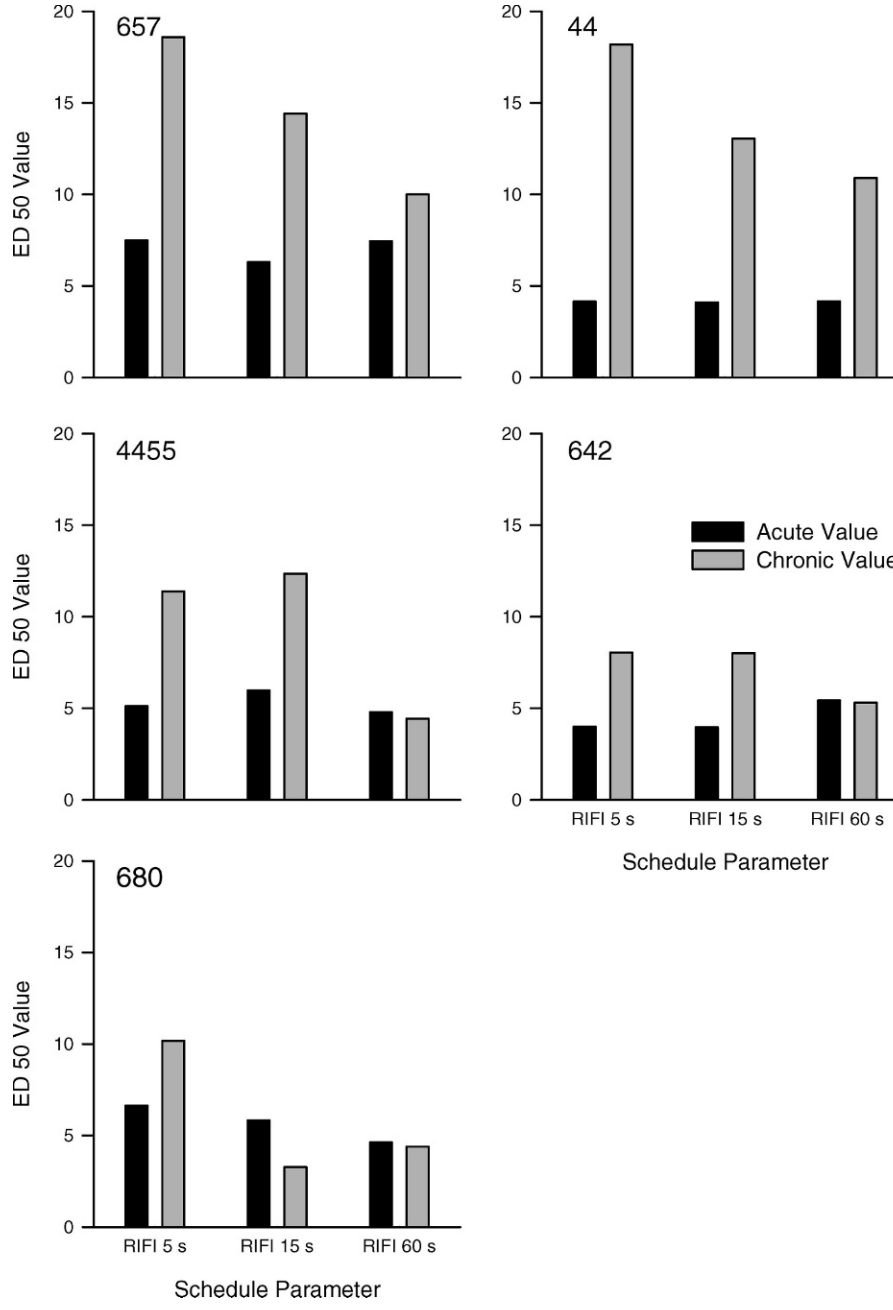

Fig. 2. ED_{50} values (in mg/kg) for acute and chronic dose assessments are presented. Black bars represent acute values and gray bars show chronic-assessment values. See text for details concerning estimates of the ED_{50} values.

factor in the formation of tolerance related to schedule size.

Under FR schedules and RIFI schedules, the length of the PRP has no direct influence on the subsequent delay from the end of the PRP until reinforcement. This is because reinforcement in ratio schedules is dependent on the completion of a predetermined number of responses, and once initiated responding typically occurs at a roughly constant rate (Ferster & Skinner, 1957). Reinforcement in an RIFI schedule depends on the subject

making one response to initiate an FI, which the animal then satisfies by making a second response after the allotted time has passed. In both cases the PRP does not alter the delay from its end to the next reinforcer presentation. On the other hand, the PRP is included in the delay to the next reinforcer in FI schedules. In the case of interval schedules the inclusion of PRP in the total delay to reinforcement may create contingencies that are likely to allow the development of tolerance. Consider what might have happened when response rate was reduced by drug. Under FI schedules (or short FR and RIFI schedules), ending relatively long pauses is followed by a relatively short delay to reinforcement, a condition that likely promotes recovery of responding. On the other hand, RIFI and FR schedules do not provide any such opportunity when the parameter value is sufficiently large (Table 1).

Previous studies that have resulted in equivalent levels of tolerance across schedule parameters have all had equivalent requirements on numbers of responses across schedules (Branch, 1990; Pinkston & Branch, 2004; Schama & Branch, 1989). One possible interpretation of these findings is that the equal magnitude of tolerance across components was due to the low, but comparable response requirements. Consistent with such a view is that in experiments with ratio schedules, tolerance was evident with small response requirements, but not with larger requirements (e.g., Hughes & Branch, 1991; Hughes, et al., 2005; Nickel, et al., 1993; van Haaren & Anderson, 1994). The results of the current study cast doubt on that view, because the response requirement was held at two for all schedules, and the resulting tolerance was nevertheless modulated by schedule duration. With that said, it should be noted that it was rarely, if ever, the case that only the minimum of two required responses were emitted. In fact, Table 1 illustrates that for all animals, amount of responding was directly correlated to RIFI parameter. A study using a response-initiated fixed-time schedule (RIFT) might eliminate the relationship between schedule parameter and number of responses emitted, with PRP almost totally isolated for examination.

In contrast to the above reports, Dallery and Lancaster (1999) found that 4 of 8 rats showed tolerance to effects of amphetamine on behavior under a five-component VI schedule that was apparently schedule-parameter related. Dallery and Lancaster used a procedure with fixed time periods of exposure to each VI schedule, which resulted in substantially different numbers of reinforcers (ranging from an average of 2 to an average of 60 reinforcers per 10-min exposures) in each schedule component. That difference in procedure, which has yet to be explored in subsequent research, may be responsible for the differing outcomes. It remains the case, nevertheless, that when numbers of reinforcers have been held constant, schedule-parameter-dependent tolerance has been observed consistently with ratio schedules, but rarely with interval schedules.

Examination of Table 1 reveals that the percentage of the IRI spent pausing was greatest in the RIFI 60-s component and shortest in the RIFI 15-s component. Concomitantly, the response rates for 3 of the 6 pigeons were greatest in the RIFI 15-s component. These data are consistent with the view that the RIFI schedule produces behavior in some respects similar to that observed under FR schedules. Higher response rates in the RIFI 15-s schedule than in the RIFI 5-s schedule are consistent with research examining response rate and FR value. Specifically, a previous comparison of relatively short FR schedules, ranging from FR 1 to FR 20, showed that response rates increased as the requirement increased (Boren, 1961), and it is known that at larger ratio values, response rate decreases as ratio increases (e.g., Felton & Lyon, 1966). Table 1 shows that the average number of responses per reinforcement for all subjects in the RIFI 15-s component was less than 20, thus falling into the previously examined range. Furthermore, a similar pattern of response rates was observed in the Hoffman et al. (1987) study. That is, the highest rates of reinforcement occurred in the middle FR value (FR 25). The function relating response rate to RIFI value, therefore, is similar in form to the function relating response rate to FR value. That outcome, too, testifies to the functional similarity of FR and RIFI schedules.

For Subject 611, there was relatively little change in response rate after acute administration of the larger doses (10.0, 13.0, & 17.0 mg/kg). Following chronic administration of 10.0 mg/kg the response-rate increases

initially observed at the low doses under the RIFI 60-s schedule were attenuated. Along with the tolerance to rate increases observed, there was an overall decrease in responding during the chronic phase. Such an outcome is not entirely uncommon in the literature on effects of chronic cocaine on operant performance (e.g., Branch, 1990). Two possible contributing factors were the subject's initial insensitivity to the acute effects of cocaine and the relatively high chronically administered dose of cocaine. Both reduced initial sensitivity (Stafford & Branch, 1996) and magnitudes of chronic dose (Branch, Wilhelm, & Pinkston, 2000) have been associated with sensitization to cocaine's effects on operant performance in pigeons. (For a discussion of this issue see Grabowski & Dworkin, 1985.) Subject 611's data, therefore, are consistent with earlier findings.

To summarize, the current study found schedule-parameter-related tolerance under a modified FI schedule. In doing so, it confirmed that a lack of relationship between PRP termination and delay to reinforcement, as exists under FR schedules, can be correlated with the observation of parameter-related tolerance. Thus, the current results suggest that the differences in findings with multiple FI and multiple FR schedules (e.g., Hoffman et al., 1987 vs. Schama & Branch, 1989) have been due to an important difference between the two schedule types other than the contingencies at the moment of reinforcement. Specifically, the fact that FR (and the current RIFI) schedules enforce a delay between the response that ends the PRP and the presentation of reinforcement, whereas FI schedules do not, appears to be an important determinant in the magnitude of tolerance that develops as a result of chronic exposure to cocaine. The role of delay to reinforcement following the termination of PRP therefore seems to be a likely correlate of the development of this pattern of tolerance.

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APPENDIX

Mean response rates (r/s), postreinforcement pause(s), and running rates (r/s) for all saline sessions.

Subject	Response Rate			Postreinforcement Pause			Running Rate		
Prechronic	RIFI 5 s	RIFI 15 s	RIFI 60 s	RIFI 5 s	RIFI 15 s	RIFI 60 s	RIFI 5 s	RIFI 15 s	RIFI 60 s
680	1.13	1.32	1.10	1.27	2.43	26.07	1.39	1.02	1.48
642	3.61	2.61	0.69	1.80	2.90	30.70	4.84	3.08	1.00
611	2.18	2.20	0.75	1.37	2.20	26.13	2.39	1.93	1.67
657	1.18	1.84	1.13	1.67	2.73	35.47	1.17	2.02	1.71
44	1.62	1.07	0.49	1.40	6.05	37.65	2.03	1.44	0.77
4455	1.46	1.22	0.46	1.00	1.50	27.15	1.80	1.30	0.66
Chronic									
680	0.72	1.57	1.01	1.75	2.90	19.20	0.53	1.00	0.67
642	3.35	2.34	1.05	1.43	4.00	24.73	4.20	2.86	1.42
611	0.95	1.39	0.93	2.70	3.05	18.78	1.21	1.61	0.99
657	0.96	1.49	1.15	1.75	2.25	18.60	1.20	1.77	1.66
44	1.57	1.21	0.59	1.40	4.25	33.45	1.68	1.51	0.63
4455	1.63	1.29	0.50	1.77	2.50	15.83	1.89	1.27	0.63